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THE DYNAMICS OF HAEMOPOIESIS*

BY

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Even the most casual survey of the activities of the haemopoietic system, which has to maintain a constant population of erythrocytes, leucocytes, platelets, and other factors in the face of losses caused by daily wear and tear, can leave no doubt that the system is highly dynamic. It is perhaps not inappropriate that I should have chosen this title for the Thomas Huxley Lecture, since Huxley himself, who qualified from this great school in 1845, was a most dynamic personality. I propose to present, in a necessarily most limited survey, a few of the active features of the haemopoietic system in the light of my experiences and work, as well as my considered opinion of the work of others; and I shall try to make some estimate of the nature and magnitude of the task of providing and renewing a normal population of blood cells. This will necessarily call for some survey of the physiological processes of blood formation.

It is fortunate, perhaps, so far as dynamic studies are concerned, that the many mobile cells of the haemopoietic system have an unmistakable appearance or a unique composition which enables something of their life histories to be accurately followed by cytochemical, serological, and radioactive techniques, and by these means some estimate has been made of what is required in everyday life, as well as in times of stress.

The active bone marrow in the average adult is estimated to weigh some 3,000 g. (3.5–6% of body weight, or 1,500–3,500 g.); it roughly equals the weight of the liver; its volume is large, being some 70 ml. at birth and about 4,000 ml. when the subject is full-grown. In the adult, however, only about half the marrow is in an active state, but it has an enormous reserve of functional capacity, as well as considerable room for expansion. The parent cells of the marrow can produce many times their own volume of mature cells in a relatively short time.

The Erythron

So far as the erythron (Fig. 1) is concerned the 3,000 g. of bone marrow makes use of the amino-acids derived from the protein pool and of iron derived from the catabolism of effete red cells, as well as some of that which is absorbed from the intestine, and a little of that which is contained in the iron stores, in order to maintain a circulating erythrocyte population of some 25 million millions (25×10^{12}).

There is good evidence that in a normal person the life-span of the red corpuscle is some 120 days.

The task of maintaining the erythrocyte population, the replacement of 1/120 each day, amounts, therefore, to approximately 2.1×10^{11} corpuscles a day, or about 9,000 millions in an hour. This involves the incorporation of 6.5 g. of haemoglobin (each gramme containing 3.34 mg. of iron) a day on the production side, whilst the daily destruction of cells leads to the liberation of about 20–26 mg. of iron, together with porphyrin and globin.

The process of red-cell destruction is carried out by the reticulo-endothelial system, itself being about half the weight of the marrow, from whence the iron and globin are used again, whereas the porphyrin pigments, appearing in the bile, are excreted mainly in the faeces as some 250 mg. of faecal urobilinogen a day. Excretion, however, is very variable, and it is difficult to obtain correlation between corpuscular destruction and pigment excretion.

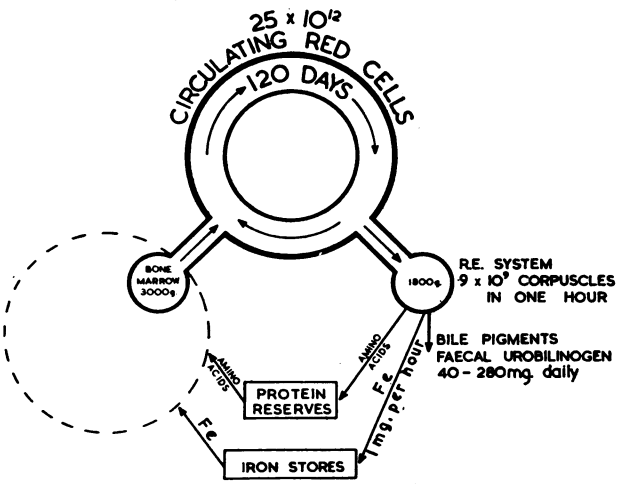

FIG. 1.—The erythron (after Wintrobe).

On the other hand, the amount of iron which is excreted is minimal, and is fairly precisely known, being a daily amount of from 0.6–0.8 mg. in the bile (Hawkins and Hahn, 1944) and 0.4–0.6 mg. in the urine (Barer and Fowler, 1937) according to sex. In all estimations, however, the fact that women suffer an iron loss of 10–40 mg. at each menstrual period, or about 1 mg. a day over the whole menstrual cycle, has to be borne in mind, since it means that women lose about twice as much iron as men.

Pregnancy, a physiological process, almost doubles the figure, but lactation adds no more than 1.5 mg. to the normal daily loss, unless menstruation becomes re-established, whereupon the total iron loss becomes almost as great as in pregnancy.

In effect, some nine-tenths of the dry weight of the red cell consists of haemoglobin, and this is contained in a complex stroma, itself a unique combination of

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protein and lipids together with such specific factors as blood-group substance as well as enzymes, minerals, and other substances. The whole comprises a cell which is one of the most specialized structures in the mammalian organism, a cell whose functional activity is carried on for months after its nucleus has been lost, and with such efficiency that it consumes practically none of the oxygen which it transports.

This simplified and elementary summary of the everyday dynamics of erythropoiesis underlies the basic pathology of all anaemias, for when the pace is not maintained then anaemia occurs—that is, when blood loss or blood destruction outstrips the daily production (Whitby, 1937). And the principle is the same whether the blood loss is obviously direct, as with haemorrhage or a violent haemolytic process, or whether it is no more than the physiological hourly blood loss of some 9,000 million cells, to which I have already referred.

Failure to keep pace with the physiological blood loss may be due to very many causes. Some of these are trivial, some are serious, some curable, others incurable, and they may operate with different intensities, and singly or in combination, to reduce the efficiency of the process of blood formation to various degrees; these causes include everything in the vast field of what used to be called secondary anaemias. A proper understanding of these different stresses demands some knowledge of the processes involved in haemoglobin synthesis, iron balance and metabolism, red-cell production, and red-cell maturation.

Haemoglobin Synthesis

The synthesis of haemoglobin requires supplies for the formation of the sub-units and the building up from these of the main components of haemoglobin; in this process enzymes, hormones, vitamins, and other substances play a large part. Globin is synthesized from natural amino-acids; its availability is not usually impaired except by gross dietary deficiency of one or more of the ten essential amino-acids. Moreover, the deficiency has to be sustained and severe before globin formation is reduced, because the body preferentially breaks down even its own proteins to provide amino-acids for haemoglobin formation, rather than that there should be a globin deficiency. Tissue respiration is indeed a primary vital function.

The synthesis of haem requires adequate supplies of porphyrin precursors and of iron. Two porphyrins (I and III) are found in nature and in the animal body. In the human subject these porphyrins are synthesized and are not, as in some animals, derived from preformed pyrroles such as chlorophyll.

When haemoglobin is catabolized the porphyrins are not used again as such, but the iron which they contain is mainly conserved and, indeed, forms the major part of the iron used for the daily requirements of haemoglobin, since it appears to be preferentially used before either the iron which is absorbed from the intestine or that which is contained within the body stores. Nevertheless, as a protection against stress, the iron reserves of the body are very considerable, a fact which becomes obvious when one realizes the speed with which a patient who has suffered a moderate haemorrhage can regenerate his blood without supplementary iron treatment.

Iron Stores

Hynes (1949) found that the iron stores in a normal man probably amounted to some 600 mg., which is sufficient to replace about one-quarter of the circulating haemoglobin in times of need. This estimate agrees with the clinical observation that a haemorrhage of roughly this order is the largest amount from which recovery is readily possible without supplementary iron treatment.

We have made a fairly close study of children in my department in order to arrive at some estimate of the amount of iron required by growing children to furnish an adequate tissue store. Because the blood volume increases with growth and because the tissue stores likewise enlarge, the growing child requires considerably more iron than the adult. We have estimated that infants, during the first year of life, need to lay down an additional store of some 200 mg. of iron, the amount falling to 100 mg. annually in the third year, and remaining at this figure until about the ninth year, when growth begins to increase rapidly. The amount of iron then laid down rises to about 350 mg. at the age of 17, and thereafter declines to zero at 21, when growth ceases.

The building up of iron stores is, however, by no means a straightforward process, since the manner in which iron is absorbed from the intestine and the form in which that which is derived from the catabolism of red cells or from intestinal absorption is transported to the various stores within the body, or, from the stores, to be incorporated in the haem molecule, is one of the processes in iron metabolism which are by no means simple.

Transport of Iron

At any one time the total serum iron of a normal man is about 4 mg., whilst every day some 20–26 mg. of iron leaves the blood stream, and of this about four-fifths is taken up by the marrow. This is used for the immediate daily requirement in haemoglobin synthesis, whilst the excess is stored primarily and mainly in the liver. In order to transport the amount of iron required for normal daily haemoglobin synthesis the iron in the plasma must therefore be turned over some five times a day.

The marrow is very active in removing serum iron from the blood. Theoretical calculations suggest that during increased haemopoietic activity more than 10% of the plasma iron passing through the bone marrow may be retained (Laurell, 1952), and since this iron in process of transport—so-called Fe-transferrin, a plasma-globulin—is mainly derived from the catabolism of red cells, and is rapidly used again, it follows that the iron stores of the body are turned over relatively slowly. The main cycle of iron turnover is from the plasma to the newly formed cells and from the old catabolized cells back to the plasma.

Thus the level of plasma iron in the blood represents an equilibrium among a number of dynamic processes which include the rate of haemoglobin breakdown and the release of iron therefrom, the rate of uptake of iron by the marrow for the synthesis of haemoglobin, the rate of removal of iron from the blood stream for storage in the tissues, the rate of formation and decomposition of transferrin itself, as well as the degree to which it is saturated with iron. This last point enters into the field of practical clinical medicine, since the level of plasma iron and the degree of iron saturation are considered to be sensitive and reliable indices of iron deficiency or iron excess.

For example, it is generally found that transferrin is saturated with iron in diseases, such as haemochromatosis, in which iron is in excess; or when haemoglobin catabolism is active, as with the haemolytic anaemias; or when the marrow needs iron but cannot use it properly, as with pernicious anaemia.

On the other hand, transferrin remains very unsaturated with iron when the bone marrow is highly active in a physiological manner, as with acute haemorrhage and iron-deficiency anaemia.

Absorption of Iron

From the aspect of physiology, as well as practical therapeutics, the control of iron absorption represents one of the key points in iron balance and iron metabolism. This likewise is not simple. A single guiding principle determines

the maintenance of iron balance—namely, that to the human body iron is a precious metal which is carefully conserved. Excretion is minimal.

Iron balance is maintained by a regulation of absorption according to the needs of the body, rather than by the excretion of unwanted excess. If this were not so, then every aged person would suffer from haemochromatosis. Sufficient iron to balance the small daily excretion is ordinarily derived from everyday foodstuffs, some of which contain reasonable quantities of the metal and others a negligible amount, and there is abundant evidence (Moore *et al.*, 1944) that ferrous iron is absorbed twice as effectively as ferric.

Without entering into detail, one may say that in certain foods iron is more available than in others, that valency and reaction, such as the difference between achlorhydria and normochlorhydria, affect absorption, and that an iron-free protein in the intestinal mucosa—apoferritin—can become appropriately and variously saturated with iron to form ferritin, according to body needs, until no more can be absorbed. This enters the plasma to contribute to the transferrin therein, and to be deposited therefrom in the tissue depots as ferritin once again.

It is instructive to note that, in experimental iron-deficiency anaemias, neither ferritin nor apoferritin can be detected in the cells of the intestinal mucosa, but that both quickly appear when iron feeding is instituted. This leads to the attractive theory that apoferritin is specifically formed in response to the stimulus supplied by the presence of ionized iron in the gut.

It would seem that ionic iron in the mucosal cell is in equilibrium with the plasma iron and this, in turn, with the iron in ferritin in the store depots. Thus, when the ionic iron in the mucosa attains a certain level, a state of mucosal block occurs and continues until the level of ionic iron in the cells falls low enough to allow more iron to be absorbed.

Utilization of Iron

Because of all the factors which govern the movement and utilization of iron, it is not easy to translate practical therapeutic principles into simple mathematical expressions, since the theoretical requirements are greatly influenced by such matters as absorption, route of administration, the nature of the preparation, and the extent to which its iron content is utilized.

An adult with 100% of haemoglobin has from 750–900 g. of circulating haemoglobin containing from 2.5–3 g. of iron. In order to replenish each 1% of haemoglobin deficiency, the body must absorb and utilize some 25 mg. of iron. Ferrous salts, the best preparations, are used only to the extent of about 15%. One gramme of anhydrous ferrous sulphate contains 360 mg. of iron, and if 10% of this is utilized the administration should cause a rise of about 2% in the circulating haemoglobin.

Practical experience has shown that there is no advantage in giving more than 2 g. of ferrous sulphate a day, which ought to ensure a rise of 4%. It is not justifiable, however, to assume that iron given to anaemic patients in optimal doses will be absorbed in accordance with the theoretically expected utilization; in that, with iron deficiency, it is often absorption which is at fault.

Many patients also do not respond to ingested iron, and it is quite useless to increase the dose beyond the optimum. On the other hand, with intravenous iron, the whole is absorbed and is rapidly available for utilization provided the pathological process is not such as to inhibit it.

In some circumstances the utilization may amount to as much as 80% (Whitby, 1949), causing an apparent increase in haemoglobin of threefold or more. I have deliberately said "apparent," since every now and again we become aware of the fact that figures obtained from samples of the peripheral blood are relative rather than absolute, and that they may be fallacious unless they are converted into total figures by means of a blood-volume determination.

Table I (a case of gross iron deficiency) is a simple illustration of this point, since it reveals the fallacy of estimating iron utilization by the peripheral blood figure alone without

TABLE I.—*Absorption and Utilization of Iron in Patient Weighing 50 kg. (Ferrous Sulphate=600 mg. Iron Daily)*

Day of Treatment:	0	9	23	49
Hb (g. per 100 ml.) ..	6·7	8·3	10·5	13·3
Increase Hb	—	24%	5·7%	100%
Plasma vol. (ml.) ..	2,120	2,250	2,410	2,100
Corpuscular vol. (ml.)	710	1,060	1,290	1,590
Total blood vol. (ml.) ..	2,830	3,310	3,700	3,690
Total Hb (g.)	190	280	390	490
Increase in total Hb ..	—	47%	105%	160%

reference to the total haemoglobin as determined by the blood volume. Whereas the former shows an increase of the order of 100% (from 6.7 to 13.3 g. per 100 ml.), the latter shows the true increase to be 160% (from 190 g. to 490 g.).

In theory, a patient with pernicious anaemia should have no need for iron, in that the haemoglobin was once normal and almost all the iron derived from the cells during the course of destruction is retained in the body. But we (Whitby and Britton, 1953) have found that some 40% of patients with pernicious anaemia require iron as judged by the mean corpuscular haemoglobin concentration, and, so far as women are concerned, a great number are iron-deficient before they contract pernicious anaemia.

Table II shows the very large amount of iron that is utilized during the cure of pernicious anaemia, as well as the adjustments in corpuscular and plasma volumes which

TABLE II.—*Iron Requirements in Pernicious Anaemia. Female Weighing 45 kg.*

Day of Treatment:	0	50
Haemoglobin (g. per 100 ml.) ..	3·9	14·0
Plasma vol. (ml.)	3,070	2,300
Corpuscular vol. (ml.)	400	1,500
Total blood vol. (ml.)	3,470	3,800
Total haemoglobin (g.)	130	530
Total iron (mg.)	434	1,770

occur at the same time; the patient, a small woman of some 45 kg., used as much as 1.34 g. of iron with a four-fold increase in total haemoglobin, and at the same time an initial high plasma volume became readjusted to a lower figure coinciding with an increase in corpuscular volume, though the total blood volume remained virtually the same.

It is unfortunate that there is no simple method, indeed no method entirely free from fallacies and objections, for the determination of blood volume, since an accurate appreciation of the movements and alterations in cells and plasma would be of great value in clinical medicine.

Erythropoiesis under Stress

The examples which I have given illustrate some of the features associated with the utilization of iron, but they also serve to show that even under apparently straightforward conditions the mathematics of iron balance may be complex.

Numerous factors may indeed intrude to upset a simple calculation, and even though as a basic principle it can be accepted that many anaemias are due to the fact that production fails to keep pace with the physiological but negative side of the iron-balance equation, it is axiomatic that a gross negative imbalance could not endure for long, otherwise the subject would soon have no red cells at all. This can be well illustrated by the dynamic activity that lies behind the clinical syndrome of haemolytic anaemia.

If the volume of the circulating cells is to remain constant, then production and destruction must be equal, even though the organism may need to adapt itself to a diminished population or to a population of cells ill-equipped to perform their proper function, assuming that both such

populations are composed of cells having a normal survival time.

When the negative side is rapidly increased, as with blood loss or violent haemolysis, balance can be maintained only by compensatory hypertrophy. When, therefore, as is usual in many of the haemolytic anaemias, the average red cell survives for a significantly, sometimes very considerably, less time than the normal average of 120 days, the degree of compensatory hypertrophy needs to be great, and may, indeed, be more than the latent reactive powers of the marrow can accomplish.

Crosby (1954) has given some instructive figures illustrating this point. Thus the function of the red marrow is to maintain a constant level of circulating red cells, and for this purpose, to quote Crosby, "Ten red cells that survive twelve days are equivalent to one red cell that survives 120 days, so that, to maintain a normal level with short-lived twelve-day erythrocytes the marrow would have to produce each day ten times the normal number."

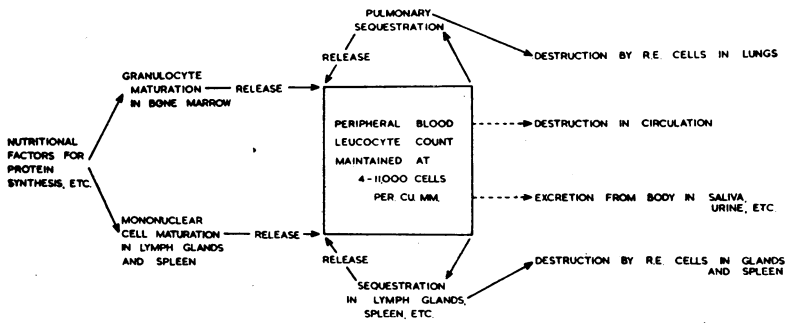

FIG. 2.—The maintenance of a normal level of circulating leucocytes.

In certain circumstances, both factors—red-cell survival and marrow function—may contribute to the production and maintenance of a severely anaemic state—namely, cells which have a short survival time, which are destroyed by random selection rather than by virtue of age, and a marrow which is incapable of an adequate response.

Another example is pernicious anaemia, when the life-span of the red cells is about 30 days (about one-quarter of the normal period), and it is perhaps difficult to appreciate that even though the bone marrow utilizes as much as 17 g. of haemoglobin a day, or two and a half times normal, the hypertrophy is insufficient to maintain the red-cell count at a normal level.

In congenital haemolytic icterus the utilization of haemoglobin by the hyperplastic marrow is even greater. This is because the spherocytes have the short survival time of some 12 days only, and because at times of an aregenerative (sometimes called aplastic) crisis the marrow cannot keep pace with the demands. The degree of anaemia may then rapidly become severe.

The Leucon

Leucopoiesis is also highly dynamic. The number of leucocytes needed to replace daily losses and maintain the circulating cells within the normal range has been studied frequently and by many methods, but the estimates made of the normal life-span of the different leucocytes vary widely. Studies in parabiotic rats (van Dyke and Huff, 1951) gave times as short as 23 minutes for the average neutrophil and 170 minutes for a lymphocyte. White (1954), however, estimated the intravascular life-span of transfused neutrophil leucocytes, tagged with mepacrine, to be from 30 to 90 minutes.

At the other end of the scale, when using radioactive phosphorus, the average survival time of the neutrophil polymorphonuclear in a normal subject was estimated (Kline and Cliffton, 1952) to be thirteen days. Many other intermediate values have been obtained by different methods, and it is not possible in the present stage of knowledge to make more than a rough estimate of daily leucocyte loss. The lowest figure must be of the order of 1,000 million leucocytes, and the highest may be as much as a million million. But as an approximate compromise, if it be accepted that the life of the neutrophil polymorphonuclear does not exceed five days, it is necessary for the marrow to replace at least some 5,000 million neutrophils each day, and if lymphocytes have a life-span of less than one day then the daily replacement figure needs to be some 3,000 millions.

With leucocytosis and leukaemia, in which the circulating leucocytes are greatly increased in number, the task of production is probably more exacting, though there is some evidence (Kline and Cliffton, 1952; White, 1954) that the life-span of leukaemic leucocytes is several times that of the normal cell.

Leucocytic production, whether physiological or pathological, demands the synthesis and new formation of the basic fundamental substances comprising the cell. Cytochemical studies have shown that multiplication is associated with an intensive production of protein within the cells.

Granular leucocytes also contain considerable amounts of phospholipids and glycogen, as well as numerous enzymes, including trypsin, lipase, amylase, catalase, alkaline phosphatase, esterase, and oxidase.

Some of the factors concerned with and the processes involved in maintaining a normal leucocyte count are shown in Fig. 2. In general, there is a balance between production by the marrow and reticulo-endothelial system; sequestration in the lungs, lymph nodes, and spleen; and destruction in these same sites as well as in the circulation itself.

Nutritional Factors in Leucopoiesis

Nutritional deficiencies of various kinds have been found to cause defective formation of leucocytes under experimental conditions.

Several investigators (Daft, 1947; Guggenheim and Buechler, 1949) found that a protein-free diet would produce severe leucopenia in experimental animals which could be corrected with a diet containing optimum amounts of protein or amino-acids. The effectiveness of different proteins for regenerating leucocytes under such experimental conditions appears to bear some relation to efficiency in growth promotion, suggesting that the same amino-acids are necessary for growth as for leucopoiesis. Deficiencies of tryptophan (Cartwright *et al.*, 1945), pantothenic acid (Ashburn *et al.*, 1947), and riboflavine (Endicott *et al.*, 1947) will cause leucopenia which can be corrected with folic acid. Presumably the leucopenia of pernicious anaemia is due to a nutritional deficiency, since it responds to treatment of the disease with folic acid, citrovorum factor, or vitamin B_{12}.

Control of Leucopoiesis

The mechanism for the physiological control of leucopoiesis is unknown. Nervous and hormonal factors have been surmised, but there is little experimental or clinical evidence in support of such views. Corticotrophin and adrenal corticoids appear to influence the peripheral leucocytes in some way, but Rosenthal *et al.* (1951) found no alteration in bone-marrow cellularity or differential cytology as the result of treating human subjects with these steroids. Nevertheless, both corticotrophin and cortisone sometimes have a stimulating action on the marrow in cases of agranulocytosis.

The question of the existence of a splenic hormone is of interest, but the available evidence, such as the large leucocytosis which immediately follows splenectomy, suggests that any splenic controlling effect is on release of cells into the circulation rather than directly upon production and maturation.

For the past fifteen years Menkin (1940, 1949) has consistently studied certain substances present in inflammatory exudates, which affect not only the maturation of leucocytes but also their release into the circulation. These leucocytosis-producing and leucopenia-producing agents have, in Menkin's hands, caused hyperplasia and hypoplasia of myeloid marrow elements when injected into experimental animals. No physiological counterparts are known.

The mechanism controlling the release of leucocytes into the circulation is little understood, but it would appear to be intact, if not overactive, in the aleukaemic forms of leukaemia (Whitby, 1951) and in the refractory anaemias associated with a paradoxically hyperplastic bone marrow (Whitby, 1952). The concept of hypersplenism and the rationale of its treatment with splenectomy implies, in fact, that the spleen has the power of regulating the release of all types of cells. Splenectomy, for any reason, may cause a considerable leucocytosis which may persist for years, but a leucocytosis does not occur in parabiotic animals unless the spleen is also removed from the second partner (Palmer *et al.*, 1951).

The interpretation of such results is, however, not always straightforward, as, for example, with the increase in circulating leucocytes which follows upon the injection of adrenaline. A critical examination of the cells in adrenaline leucocytosis shows no shift to the left in the Arneth count, and it would seem that the increase in cells is due to release of white cells from various sites of sequestration (Fig. 2) rather than to direct stimulation of or release from primary sites (Smith and Hayhoe, 1951). It may well be that the leucocytosis and leucopenia-producing factors of Menkin act also by controlling release of cells, as well as by stimulating a change in marrow activity.

Nucleic Acid Metabolism

Most, if not all, of the cells of the haemopoietic system have developmental processes in common, involving the synthesis and incorporation of substances less specific than the iron which is the essential constituent of haemoglobin, and which provides such an excellent marker for radioactive studies. Nevertheless, many of the highly differentiated cells have a unique composition, and all have intricate enzyme systems. A considerable speed in cell multiplication is obviously essential in order to replace daily wear and tear.

The vital chemistry of both red cells and leucocytes is concerned with nucleic acid metabolism. The nuclei and the cytoplasm of the young actively growing cells contain nucleic acids in high concentrations which are attached to proteins as nucleoproteins. These, in general, fall into two groups—the ribosenucleic acids with a sugar component of the pentose series, and desoxyribosenucleic acids with a sugar component of the desoxypentose series.

Cellular growth and active multiplication obviously depend upon the new formation of these fundamental substances within the cell, the nucleoproteins being the controlling factors, in that the energy necessary for synthesis is available within the molecular structure of nucleic acid.

Mitosis of marrow cells can proceed very rapidly when required, but it is not known whether a demand causes an increase in the number of cells undergoing mitosis, or shortens the time interval, or accelerates the process. Bone-marrow activity can be observed directly and the histological changes accurately described, and these in turn can be expressed roughly in terms of basic chemistry by cytochemical methods of staining.

The nucleoli and cytoplasm of blood cells contain ribosenucleic acids, and in the cytoplasm the ribosenucleic acids are found especially in the mitochondria, which are the site of enzymatic activities and probably serve as centres for protein synthesis.

The ribosenucleic acids of the nucleoli and cytoplasm appear to be concerned not only with the proliferation of young marrow cells but also with the synthesis of their characteristic cytoplasmic contents—namely, haemoglobin in the red-cell series and complex enzyme systems in the specific granules of the leucocytes (White, 1947); ribosenucleic acid diminishes as these specific substances appear (Thorell, 1947b).

The Feulgen reaction shows that the nuclei of early cells, particularly the chromatin and chromosomes, are rich in desoxyribosenucleic acid, especially during the period of active division of the cells, when it may well provide the energy necessary for the protein synthesis which takes place at this time.

The widely distributed enzyme alkaline phosphatase, which is found in normoblastic nuclei, is formed in large amount around the nucleus during active blood regeneration. The nucleus becomes infiltrated with the enzyme, after which pyknosis, fragmentation, or extrusion occurs. It is believed that alkaline phosphatase is intimately concerned with nuclear destruction. During active haemopoiesis, also, the magnesium content of the red cell is increased (Dahl, 1950), which is of interest since magnesium is a potent activator of the phosphatases.

A balanced production of the cells of the bone marrow clearly depends upon a carefully regulated chemical system, and since nucleic acids appear to govern cell division the differences in their concentration or availability may even determine the proportions of red and white cells in the blood. In certain pathological conditions there may be competition within a cell or between cells for substances which are essential for maintaining normal equilibrium.

The importance of these basic facts in practical haematology becomes clear as advances are made in knowledge concerning the factors essential for blood formation, as well as the manner in which these factors act. It is significant, for example, that thymine and thymidine have a haematological therapeutic action, whilst folic acid, citrovorum factor, and vitamin B_{12} may exert their essential activity as coenzymes for certain stages in the synthesis of nucleic acid from simple substances (Fig. 3).

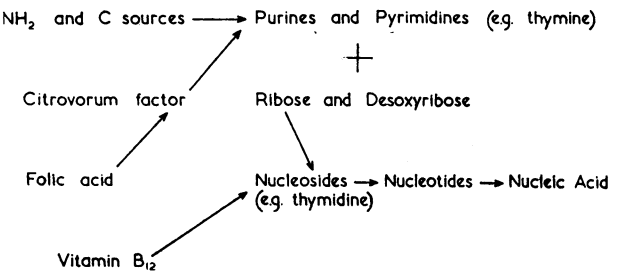

FIG. 3.—Scheme for the synthesis of nucleic acids from simpler substances, with suggested points of action of certain haemopoietic substances.

Abnormal Haemopoiesis

In some pathological processes the deviations from normal may be explained, or at least expressed, in terms of alteration in the normal rhythm. In other conditions the mode of action of an apparently specific material such as vitamin B_{12} or folic acid may be thought of as being due to the part it plays in the synthesis of essential cellular constituents from simpler substances, and especially in relation to nucleic acid metabolism (Fig. 3).

For example, Japa (1945) suggested that the essential abnormality in megaloblastic erythropoiesis was one involving nucleic acid metabolism preventing the proper development of nucleoli, thereby inhibiting the capacity for cell division and leading to a prolonged duration of mitosis, decreased frequency of division, earlier cessation of division, and consequent differentiation at an earlier genealogical stage.

In the marrow cells in pernicious anaemia the ribosenucleic acids of the cytoplasm and nucleolar apparatus do not disappear even when haemoglobin formation occurs (Thorell, 1947a). This is in contrast to what happens in

the normal subject, as well as in the haemorrhagic anaemias, even though haemoglobin synthesis in the latter is retarded by lack of iron. In leukaemia, leucocytes accumulate a high concentration of ribosenucleic acids in the cytoplasm and nucleoli which does not rapidly decline, as in the case of normal cells.

Desoxyribosenucleic acids are an important constituent of chromosomes, being apparently attached at specific loci in the polypeptide chain which goes to make up the chromosome fibre; the amount differs at the different phases of chromosome division, and is noticeably abnormal in certain pathological states.

Under normal conditions there is more desoxyribosenucleic acid in the chromosomes of the proerythroblast than the promyelocyte at the metaphase. In pernicious anaemia, however, the promyelocyte chromosomes contain very little desoxyribosenucleic acid, and this leads to incomplete spiralization; the proerythroblasts and early megaloblasts, on the other hand, show an excess which consequently leads to over-spiralization. Over-spiralized chromosomes are associated with irregular division, multipolar spindles, and chromatoid bridges at the anaphase. In short, it would seem that mitotic abnormalities are closely associated with different distributions of desoxyribosenucleic acid.

Conclusion

In this limited survey of some of the dynamic aspects of haemopoiesis I have naturally laid most emphasis on basic principles, some of which are now well established owing to the specific characteristics which the cells of the haemopoietic system possess. I have also paid some attention to the quantitative aspects of the subject and to some of the fallacies which may so easily intrude with hasty interpretation.

Simple quantitative aspects of haemopoiesis are indeed of such everyday application in clinical medicine that they are all too often accepted without critical analysis, without thought of possible alternative interpretation, or from a superficial viewpoint, to the neglect of fundamental principles.

Quantitative deductions cannot be accurate unless made upon unequivocal facts entirely free from ambiguity.

Leonard Huxley (1900) quotes Thomas Huxley, when writing to Charles Kingsley, as saying, "My business is to teach my aspirations to conform themselves to fact, not to try to make facts harmonize with my aspirations. Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly to wherever and to whatever abysses nature leads or you will learn nothing."

In no field of medicine is this more true than in haematology, which in its daily clinical application to the dynamics of haemopoiesis is largely quantitative and in which precise results require the most critical appraisal if they are to be properly and accurately assessed.

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ASSISTED CIRCULATION BY PUMP-OXYGENATOR DURING OPERATIVE DILATATION OF THE AORTIC VALVE IN MAN

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Interest in the clinical application of the various forms of pump-oxygenator (extracorporeal circulation or artificial heart–lung machine) is growing so rapidly, and the use of this type of apparatus in man has so seldom been followed by recovery, that it is customary for isolated examples of its use to be reported (Dennis *et al.*, 1951; Dogliotti, 1952; Gibbon, 1953; Dodrill *et al.*, 1953; Helmsworth *et al.*, 1953).

Three authors, Dogliotti (1952) in Turin, Gibbon (1953) in Philadelphia, and Dodrill *et al.* (1953) in Detroit, report survivors, and Helmsworth *et al.* (1952) have used an oxygenator for vein-to-vein perfusion in a case of fibrosis of the lung. The pump-oxygenator employed in the case here reported was that designed and developed by Melrose in the department of surgery of the Postgraduate Medical School. Melrose (1953a) has described the machine and Melrose *et al.* (1953b) have reported the animal experiments performed in the Buckston Browne Laboratories of the Royal College of Surgeons, which seemed to prove that the machine might be used with safety in man. The machine consists essentially of a rotating oxygenator and two rotary pumps. Its chief advantages are a high degree of efficiency in oxygenation (100 ml. of oxygen per litre of blood) and a low initial charge of blood.

The circumstances in which the machine might be used with profit in a clinical way have also been discussed (Aird, 1953), and the opinion was then expressed that the use of such a machine to by-pass heart and lung totally and to provide safely a dry heart for surgery was an aim not then immediately obtainable. We